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REVIEW ARTICLE

Galectins and cutaneous immunity

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ABSTRACT

Galectins are highly expressed in epithelial cells and immune cells. In skin, they can be detected in keratinocytes, melanocytes, dendritic cells, macrophages, and T cells. Galectins are present outside and inside the cells and thus may exhibit different functions through extracellular and intracellular actions. Galectins can be involved in the pathogenesis of inflammatory skin diseases by affecting growth, apoptosis, maturation, activation, and motility of keratinocytes and immune cells. Expression of galectins may change depending on the cellular status, such as proliferation and activation. For example, galectin-3 expression is upregulated in T cells but downregulated in dendritic cells when these cells are activated. Furthermore, their expression may also change under pathological conditions. Understanding the function of each galectin in keratinocytes and different immune cell types may reveal how galectins contribute to the pathogenesis of immune-mediated skin diseases.

Introduction

Galectins are a family of lectins containing one or two conserved carbohydrate-recognition domains (CRDs) that preferentially bind to β-galactosides.[1] Galectins are expressed widely among different organisms, including mammals, insects, sponges, fungi, and nematodes. Structurally, galectins can be classified into three types: single-CRD galectins composed of approximately 130 amino acids; double-CRD galectins containing two homologous CRDs separated by a linker of up to 70 amino acids; and galectin-3, which contains one CRD following a nonlectin region of about 120 amino acids composed of tandem repeats of short proline/glycine-rich sequences. This proline/glycine rich region is believed to participate in the formation of galectin-3 pentamers upon binding of the lectin to multivalent carbohydrates.[2] Single-CRD galectins can form homo-dimers and thus can be functionally bivalent, while double-CRD galectins are intrinsically bivalent.[3]

Galectins do not contain a classical signal sequence but can be secreted through an as yet undefined secretory pathway and detected in the extracellular space. The proteins are known to be localized in the cytoplasm and can move into the nucleus or be associated with intracellular vesicles under certain conditions.[4] The distribution of galectins between cytoplasm and nucleus depends on the cell types and proliferative status.[5] Modification of galectins, such as phosphorylation may also contribute to the subcellular localization.[6]

Since galectins can exist both outside and inside the cells, their functions may differ depending on their location. Galectins may work extracellularly in an autocrine or paracrine manner to modulate cell status or functions, e.g., activation of cells, mediation of cell–cell and cell–extracellular matrix interactions, and promotion of cell migration.[7,8] These extracellular effects may result from cross-linkage of glycoproteins on the cell surfaces due to galectins' bivalency or oligovalency with regard to carbohydrate binding. The resulting structures have been termed "galectin lattices" and their formation can alter the properties of the glycoproteins involved, for example restricted lateral mobility on the cell surface, thus modulating responses mediated through them.[9]

Intracellularly, galectins can function in a carbohydrate-independent manner to regulate cell apoptosis, migration, and responses to stimuli.[4,8] In the nucleus, galectins can be involved in pre-mRNA splicing by functioning as components of spliceosomes[10] and regulation of the expression of certain genes.[11]

Galectins in the biological responses of skin cells

Galectin-1

Galectin-1 is composed of a 14 kDa CRD and exists as monomers or homodimers. It has wide tissue distribution and is differentially expressed by different tissues in normal and pathological

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conditions.[8,12] With regard to the human skin, galectin-1 is found in keratinocytes, Langerhans cells, and fibroblasts. It is also abundantly present in the extracellular matrix in the dermis.[13]

Keratinocytes

Galectin-1 is primarily located along the plasma membrane of keratinocytes.[13] Previous studies have provided evidence that galectin-1 has the potential to mediate cell–matrix interactions by binding to cell adhesion molecules and extracellular matrix proteins, suggesting a role in cell migration, re-epithelialization, and wound healing.[14,15]

Dvořánková et al[16] showed that administration of galectin-1 had a positive effect on skin wound healing in rats. Galectin-1 can induce the conversion of dermal fibroblasts into myofibroblasts and production of extracellular matrix, thus contributing to support keratinocyte growth and promoting wound healing. However, in another study, Cao et al[17] showed that both endogenous galectin-1 and exogenously added galectin-1 do not affect the re-epithelialization rate of corneal wounds.

Fibroblasts

By immunostaining and *in situ* hybridization, galectin-1 was found to be expressed in both the nucleus and cytoplasm of fibroblasts in the dermis.[13] The expression of galectin-1 in fibroblasts has been associated with the transdifferentiation of fibroblasts to myofibroblasts and the production of extracellular matrix.[16,18]

Expression of galectin-1 in fibroblasts affects tumor progression and metastasis. Wu et al[19] found that galectin-1 knockdown decreased fibroblast activation and extracellular matrix production. Furthermore, galectin-1 knockdown significantly reduced carcinoma-associated fibroblast-augmented tumor growth and metastasis, possibly by modulating MCP-1 expression. These results suggest that galectin-1 in cancer-associated fibroblasts may be a target for cancer therapy.

Langerhans cells

In human skin, galectin-1 has also been detected in the cytoplasm and nucleus of Langerhans cells in the epidermis.[13] Fulcher et al[20] showed that galectin-1 treatment stimulated human dendritic cell (DC) maturation and triggered expression of genes related to cell migration through the extracellular matrix by upregulation of multiple matrix metalloproteinase genes. An additional study identified the underlying mechanisms and showed that galectin-1 co-clustered surface CD43 and CD45 on DCs and induced cell activation and migration through Syk and protein kinase C signaling.[21] Intradermal injection of galectin-1 also enhanced *in vivo* migration of dermal DCs to draining lymph nodes in the autoimmune MRL-*fas* mice.[21] These results suggest that galectin-1 may contribute to initiation of an immune response in part by regulating DC migration.

Galectin-3

Galectin-3 is mainly expressed in inflammatory and epithelial cells.[8] Cells expressing galectin-3 in the skin include DCs, macrophages, T cells, keratinocytes, mast cells, hair follicles, sebaceous and eccrine glands, melanocytes, and fibroblasts.[8]

Keratinocytes

Galectin-3 is present in the cytoplasm of normal keratinocytes.[22] Upon differentiation of keratinocytes, the expression of galectin-3 is upregulated.[23] Galectin-3 has been shown to be limited in the suprabasal layers of epidermis and be colocalized with desmosomal proteins.[24] These findings suggest that galectin-3 expression is associated with keratinocyte differentiation and maturation. Another study also concluded that expression of galectin-3 is correlated to the status of keratinocyte differentiation.[23] Galectin-3 binds to laminin and enhances keratinocyte cell motility.

Galectin-3 has been shown to exhibit anti-apoptosis function in ultraviolet-B (UVB) irradiation-induced apoptosis in mouse keratinocytes. UVB can induce galectin-3 expression in keratinocytes and galectin-3 suppresses extracellular-regulated kinase (ERK) activation and enhances Akt activation in apoptosis-related responses.[25] Recombinant galectin-3 has been shown to induce keratinocyte migration possibly through an extracellular interaction with β4 integrin, epidermal growth factor receptor (EGFR), and laminin on the keratinocyte matrix.[26] Our group has recently found that galectin-3 regulates intracellular trafficking of EGFR in keratinocytes. Gal3$^{-/-}$ keratinocytes have a lower expression of EGFR and this results in lower cell migration and slower wound re-epithelialization in mice.[27]

T cells

Functions of galectin-3 in T cells has been recently reviewed.[28] Extracellular galectin-3 can form lattices with the T-cell receptor (TCR) complex and negatively regulate TCR-mediated signal transduction.[29] Extracellular galectin-3 can also induce T cell apoptosis.[30] Analyses of galectins in T cell proliferation have recently shown that galectin-1 and galectin-8 can costimulate T cell proliferation, while galectin-3 fails to costimulate and instead antagonizes galectin-1- and galectin-8-facilitated T cell responses.[31] An endogenous function of galectin-3 recently shown by our group is related to its recruitment to the immunological synapse, where it can play a negative role in the T cell response upon TCR engagement.[32] The function of galectin-3 in the immunological synapse may involve its binding partner, Alix, which is associated with endosomal sorting complex required for transport.

Macrophages

Galectin-3 has been shown to activate and promote adhesion of myeloid cells,[8] function as a chemoattractant for human monocytes and macrophages,[33] and play a critical role in alternative macrophage activation.[34] Galectin-3 was found to contribute to FcγR-mediated phagocytosis of red blood cells and translocate to the phagosomes in cells that have engulfed red blood cells.[35] Galectin-3 binds to dectin-1 receptor on macrophage and affects tumor necrosis factor-α secretion in cells infected with *Candida albicans*.[36]

Dendritic cells

Galectin-3 was found to be expressed in either immature or mature DCs. Endogenous galectin-3 has been shown to drive DCs into a Th2-promoting phenotype, as gal3$^{-/-}$ DCs secrete a higher level of interleukin (IL)-12 cytokine, which is a potent Th1-polarizing cytokine.[37] Galectin-3 also plays a negative role in DC function in stimulating T cell activation.[38] Another proposed function of galectin-3 is that it can inhibit allogeneic T cell responses or induce higher levels of apoptosis in T cells through DCs.[39] Galectin-3 also affects motility of DCs as gal3$^{+/+}$ DCs migrate faster than gal3$^{-/-}$ DCs *in vitro* and *in vivo*.[40]

Fibroblasts

Expression of galectin-3 was shown to increase in proliferating fibroblasts compared to quiescent cells.[41] Since exogenously added galectin-3 can strongly stimulate colonic fibroblast growth,[42] this protein may also be able to stimulate fibroblasts in the skin.

Galectin-7

Compared to other more commonly studied galectins, galectin-7, a one-CRD galectin, exhibits a higher degree of tissue specificity;

its expression is mainly in stratified squamous epithelium and correlates with keratinocyte differentiation.[43–45]

Several studies have provided evidence to suggest a role of galectin-7 in maintenance of epithelial homeostasis. Galectin-7 was identified as an early transcriptional target responding to tumor suppressor gene p53 overexpression.[46] UVB irradiation is an efficient modulator of p53 gene expression and Bernerd et al[47] found that galectin-7 mRNA and protein were induced rapidly in keratinocytes exposed to UVB irradiation, in parallel with p53 stabilization and apoptosis induction. In addition, galectin-7 overexpression results in keratinocyte cell death. These findings suggest that galectin-7 may be related to the pro-apoptotic function of p53. Kuwabara et al[48] demonstrated that ectopic expression of galectin-7 in HeLa cells rendered them more sensitive to apoptosis triggered by various stimuli. Furthermore, galectin-7 transfectants displayed accelerated mitochondrial cytochrome c release and upregulated JNK activity upon apoptosis induction. Galectin-7 is also involved in the corneal wound healing process,[17] especially in re-epithelialization of wounds, probably through modulating corneal epithelial cell migration.[49] Such a role for galectin-7 in the homeostatic control of epithelia is supported by a recent study using galectin-7-deficient mice: Gendronneau et al[50] showed that galectin-7 helped maintain epidermal homeostasis in response to UVB irradiation and wounding by modulating keratinocyte apoptosis and proliferation as well as participating in the process of cell migration.

Villeneuve et al[51] identified galectin-7 as a new mitochondrial Bcl-2-interacting protein. A fraction of galectin-7 is constitutively localized to mitochondria, partially dependent on Bcl-2 expression. Moreover, overexpression of mitochondrial galectin-7 sensitizes mitochondria in response to apoptotic stimuli, enhancing the release of cytochrome c and Smac/DIABLO. These findings suggest that upon dissociation of galectin-7 and Bcl-2 complexes, the pro-apoptotic function of galectin-7 is uncovered, leading to the initiation of the apoptotic cascade. Furthermore, galectin-7 expression was found to be upregulated in transgenic mice expressing extracellular superoxide dismutase. The upregulation of galectin-7 may be regulated through the production of COX-2 and results in apoptosis in the epidermis.[52]

Galectin-8

Galectin-8 is a tandem-repeat type of galectin that is highly expressed in endothelial cells of lymphatic vessels compared to blood vessels and interacts with podoplanin to support the interaction of lymphatic endothelium with the surrounding extracellular matrix.[53]

The C-terminal CRD can bind to polyLacNAc glycans on T cells and cause phosphatidylserine (PS) exposure, which occurs independently of apoptosis.[54] Galectin-8 can induce T cell apoptosis via an ERK1/2-mediated pathway.[55] However, galectin-8 has also been reported to exhibit two distinct biological activities on T cells, an antigen-independent T cell proliferation and an antigen-dependent co-stimulatory effect.[56]

Galectin-8 has been shown to be expressed on platelets and induce platelet activation by binding to certain glycoproteins on platelets.[57] Galectin-8 can stimulate endothelial cell migration and capillary cell formation, and thus plays a role in angiogenesis.[58] Galectin-8 has recently been shown to play a role against bacterial infection in macrophages through induction of autophagy.[59]

Galectin-9

Human galectin-9 was first identified from the Hodgkin's disease-involved spleen.[60] At least 10-fold higher expression of galectin-9 mRNA was detected in lymphatic tissues from Hodgkin's disease patients compared to those from normal individuals.[60] Moreover, the fact galectin-9 is highly expressed in normal immune system, such as spleen, thymus, lymph nodes, and peripheral blood leukocytes,[61] suggests that it may be involved in the immune response or the pathogenesis of immune diseases.

Studies showed that galectin-9 can be produced by human T cell lines and has eosinophil chemoattractant activity.[61,62] Recombinant galectin-9 induces apoptosis in mouse thymocytes, activated CD4 and CD8 T cells, and various T, B, and monocytic cell lines.[63,64] Apoptosis in those cells through calcium-calpain-caspase-1-dependent and -independent pathways.[64,65] T-cell immunoglobulin mucin domain 3, specifically expressed in Th1 T cells but not Th2 T cells, is an effective ligand for galectin-9.[66] Binding of galectin-9 to the extracellular domain of T-cell immunoglobulin mucin domain 3 leads to Th1 cell apoptosis.[66]

Several studies have demonstrated that recombinant galectin-9 suppresses Th1 and Th17 responses, and promotes $Foxp3^{+}CD25^{+}CD4^{+}$ regulatory T cell differentiation and proliferation. In different animal models of inflammatory diseases, such as experimental autoimmune encephalomyelitis,[67] rheumatoid arthritis,[68] complex immune-induced arthritis,[69] collagen-induced arthritis,[70] allergic asthma,[71] nephritis,[72] diabetic nephropathy,[73] contact dermatitis,[74] psoriasis,[74] diabetes,[75,76] and graft versus host disease,[77] galectin-9 has been shown to have a suppressive function in Th1- and Th17-mediated immunity.

Galectin-12

Galectin-12 has been found mainly in adipocytes and plays a role in adipocyte differentiation *in vitro*[78] and lipolysis.[79] It has also been found in sebaceous gland in human skin.[80] The function of galectin-12 in sebocytes is unknown.

Figure 1 summarizes the effects of galectins on the biological responses of skin cells.

Role of galectins in cutaneous immune disorders

Galectin-1

Acute inflammation

Galectin-1 is emerging as a powerful modulator in both innate and adaptive immune responses.[8,12] In a model of acute inflammation, administration of galectin-1 suppressed bee venom phospholipase A2-induced inflammatory responses, which was correlated with diminished numbers of infiltrating neutrophils and scarce degranulated mast cells.[81] The antiinflammatory effect was also assessed *in vitro*, where galectin-1 treatment resulted in reduced inflammatory mediator release from peritoneal macrophages. Furthermore, the role of endogenous galectin-1 in acute inflammation was investigated by using $gal1^{-/-}$ mice. In a carrageenan-induced model of edema, $gal1^{-/-}$ mice displayed an attenuated edema.[82] This reduced inflammatory response was associated with lower expression of inflammatory cytokines and cellular infiltrates, and increased apoptosis of infiltrating leukocytes. The role of endogenous galectin-1 during the initiation and resolution of acute inflammation may result from the balance of different biological effects and remains to be further investigated.

Contact hypersensitivity

In addition to its role in innate immune responses and acute inflammation, galectin-1 also participates in adaptive immunity and chronic inflammation. Targeted overexpression of galectin-1 in DCs significantly increased the sensitization phase of contact hypersensitivity, while inducing a drastic inhibition of the

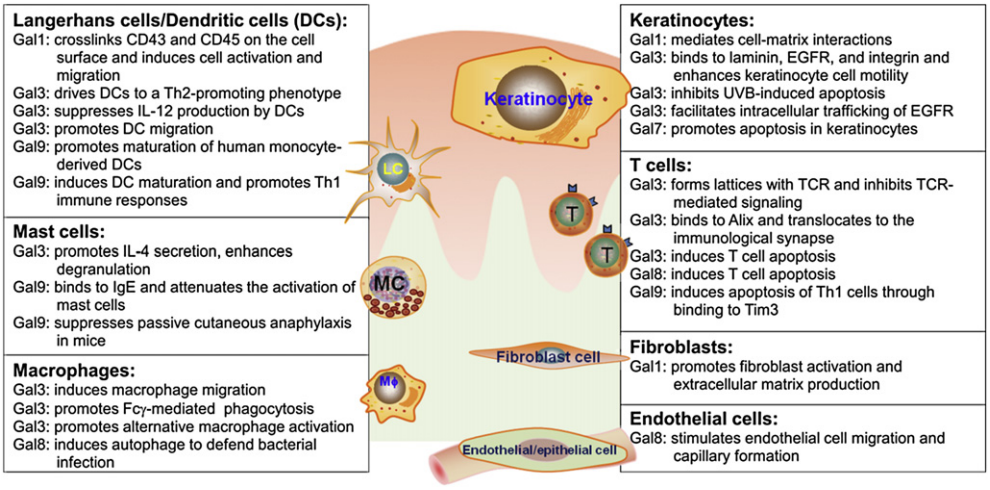

Figure 1 The effects of galectins (Gal) on the biological responses of skin cells.

elicitation phase by triggering apoptosis of activated T cells in the dermis.[83]

In a mouse model of hapten-mediated contact hypersensitivity, galectin-1-treatment alleviated T cell-dependent inflammation, and exhibited a marked decrease in interferon-γ (IFNγ)$^+$ and IL-17$^+$T cells and increase in regulatory T cells.[84] Further analyses showed that galectin-1 treatment skewed the Th2 response by upregulating IL-4 and IL-10 expression, and triggering apoptosis in the Th1 and Th17 subsets. Furthermore, Cedeno-Laurent et al[85] provided a detailed molecular mechanism by which galectin-1 exhibits immunosuppressive activity in resolving inflammatory responses. Direct binding of galectin-1 to CD45 on activated T cells stimulates IL-10 synthesis and enhances IL-21 expression through the c-Maf/AhR pathway. Galectin-1-induced IL-10-expressing T cells (termed type 1 regulatory T cells, which produce IL-10, but do not express FOXP3) effectively suppress T cell proliferation and ameliorate skin inflammation in a mouse model of allergic contact dermatitis. These results, along with the information mentioned above, suggest that galectin-1 is an anti-inflammatory mediator of skin inflammation in contact hypersensitivity.

Psoriasis

A few studies have examined the correlation between galectins and psoriasis. De la Fuente et al[86] investigated the expression and role of galectin-1 (as well as galectins-3 and -9) in psoriatic skin. Compared with normal individuals, lower levels of galectin-1 were found in both lesional and nonlesional skin samples from psoriasis patients. Galectin-1 expression was downregulated in Langerhans cells and dermal DCs as well as in peripheral blood myeloid DCs from psoriasis patients. Together with the previous studies in animal models,[87] this suggests an important role for galectin-1 in the immunopathogenesis of psoriasis. In addition, exogenous addition of galectin-1 attenuated the Th1 response, which may involve the secretion of the suppressive cytokines, such as IL-10, from DCs. It is suggested that galectin-1 downregulation may contribute to the exacerbation of the inflammatory responses in psoriasis.[86]

Galectin-1 (as well as galectins-3 and -9) is highly expressed in Langerhans cells in the skin of healthy donors. However, it is expressed at lower levels in the skin of psoriatic patients. Higher levels of Th1/Th17 cytokines were also detected in psoriatic skin.[86] The lower level of galectin-1 was considered a factor contributing to psoriasis, as exogenously added galectin-1 attenuated the Th1 response in a coculture of patient monocyte-derived DCs and autologous T cells. Blockade of the galectin-1 binding resulted in higher levels of IFNγ and lower levels of IL-10. The authors thus hypothesized that galectin-1 downregulation contributes to the exacerbation of the Th1/Th17 effector response in psoriasis patients.[86]

Galectin-3

The roles of galectin-3 in inflammation and skin diseases have been extensively studied.[7,12] These include induction of cell activation, regulation of cellular homeostasis, and promotion of cell adhesion as well as cell migration.

Atopic dermatitis

Atopic dermatitis is a chronic inflammatory skin condition that involves a predominant Th2 cytokine milieu in the initiating stages of atopic dermatitis and a mixed Th1 and Th2 pattern in chronic lesions.[88] Our laboratory has studied the effects of endogenous galectin-3 in the development of allergic skin inflammation in mice induced by repeated epicutaneous sensitization with ovalbumin (OVA). Gal3$^{-/-}$ mice did not exhibit as much epidermal thickening as gal3$^{+/+}$ mice and developed lower eosinophil infiltrations, lower serum IgE levels, and a lower Th2, but higher Th1 response compared to gal3$^{+/+}$ mice. Moreover, mice receiving gal3$^{-/-}$ T cells expressing OVA-specific T cell receptor and then epicutaneously sensitized with OVA developed a lower Th2 response and lower skin inflammation than mice that received gal3$^{+/+}$ T cells. These results suggest that galectin-3 is a proinflammatory mediator of skin inflammation in atopic skin disease.[89]

Contact dermatitis

In a study of gene expression of responses to nickel in reconstructed human epidermis, galectin-3 expression has been shown to be suppressed in epidermal keratinocytes.[90] Our laboratory has also found that endogenous galectin-3 contributes positively to allergic contact dermatitis in mice when comparing gal3$^{-/-}$ mice and gal3$^{+/+}$ mice.[40] It is possible that galectin-3 contributes to contact dermatitis through DCs, as gal3$^{-/-}$ DCs showed a reduced migratory phenotype compared to gal3$^{+/+}$ DCs.

Psoriasis

Lacina et al[91] investigated the expression of galectin-3 (as well as galectins-1 and -7) and their glycoligands in psoriatic skin compared to normal skin. Galectin-3 expression was lower in

psoriatic epithelium compared to normal epidermis. However, galectin-3 and galectin-3-reactive glycoligands were found to be strongly expressed in the capillary epithelia of psoriatic dermis, indicating that galectin-3 and galectin-3-reactive glycoligands may be involved in dermal capillary rearrangement and inflammatory cell recruitment.[91]

Galectin-9

In a mouse model of contact dermatitis, a Th1- and Th17-mediated disease, the inflammation response of ear swelling was suppressed by recombinant galectin-9.[74] In this study, recombinant galectin-9 induced apoptosis in CD4 and CD8 T cells and reduced the number of IFNγ and IL-17-producing T cells.[74] Psoriasis is another skin disease that is mediated by Th1 and Th17 responses. In the IL-23-induced psoriasis mouse model, recombinant galectin-9 reduced epidermal thickness, dermal cellular infiltrates, and decreased the levels of IL-17, IL-22, IL-6 and tumor necrosis factor-α in treated skin lesions.[74]

This suggests that galectin-9 plays a therapeutic role in psoriasis. However, the study investigating the function of galectin-9 dealt with exogenously added recombinant galectin-9. One key issue is whether endogenous galectin-9 also plays a significant role in pathogenesis of psoriasis. De la Fuente et al compared the expression levels of galectin-9 in nonlesional and lesional skin samples from 24 psoriasis patients and 10 control samples by RT-PCR analysis, but found no difference in galectin-9 expression among these samples.[86] One possibility is that galectin-9 is only expressed in specific cell types in skin tissue; therefore, the procedure was not able to detect the changes in galectin-9 expression in a subset of cells, when analyzing the whole tissues containing a mixture of cells. Indeed, when evaluating the galectin-9 expression in human skin by immunohistochemistry, Igawa et al found significant galectin-9 expression in dermal fibroblasts in the lesions of psoriasis patients.[92] Meanwhile, a significant number of eosinophils were found to be attached to dermal fibroblasts in the lesions.[92] Since it has been shown that galectin-9 has eosinophil chemoattractant activity and IFNγ induces galectin-9 expression in fibroblasts and endothelial cells *in vitro*,[93,94] it is possible that during pathogenesis of psoriasis, IFNγ produced by Th1 T cells stimulates galectin-9 expression in dermal fibroblasts and the expression of galectin-9 promotes adhesion of eosinophils in the dermis.[92]

Galectin-9 is expressed by Langerhans cells and peripheral myeloid DCs in normal human skin and blood.[86] Recombinant galectin-9 was shown to promote maturation of human monocyte-derived DCs.[95] In addition, galectin-9-treated DCs secrete IL-12 but not IL-10, and enhance the production of Th1 cytokines by allogeneic $CD4^+$ T cells.[95] Therefore, this suggests that galectin-9 is able to induce DC maturation and promote Th1 immune responses. To investigate the relationship between galectin-9 and psoriasis in human DCs, de la Fuente et al found that more severe disease indexes of psoriasis were associated with slightly lower expression levels of galectin-9 in myeloid DCs, but the difference was not statistically significant.[86]

Galectin-9 is also constitutively expressed in human epidermal keratinocytes.[92] In contrast with dermal fibroblasts, the expression of galectin-9 in keratinocytes is dose-dependently inhibited by IFNγ *in vitro*.[92] Interestingly, epidermal cells from lesions of Th2-dominated bullous pemphigoid disease showed strongly positive staining of galectin-9 in the cytoplasm of keratinocyte.[92]

Moreover, galectin-9 is expressed in a mouse mast cell line MC/9 and in human cord blood-derived mast cells.[96,97] It is known that mast cells play an important role in pathogenesis of allergic contact dermatitis.[98] Galectin-9 binds to IgE and attenuates the activation of mast cells *in vitro*.[99] Furthermore, recombinant galectin-9 suppressed passive cutaneous anaphylaxis in mice, which is an *in vivo* model for examining the degranulation of mast cells.[96] These data indicate that galectin-9 is a regulator of mast cell activity and the function of galectin-9 in mast cells might be involved in the development of dermatitis.

Taken together, expression of galectin-9 in different cell types might result in different inflammatory responses in skin. Further studies are necessary to elucidate the expression patterns and functions of endogenous galectin-9 in different cell types in different inflammatory skin disorders.

The roles of galectins in cutaneous immune disorders are summarized in Table 1.

Table 1 Roles of galectins (Gal) in cutaneous immune disorders.

Acute inflammation:
Gal 1: suppresses bee venom phospholipase A2-induced inflammatory responses
Gal 1: promotes carrageenan-induced edema
Atopic dermatitis (AD):
Gal 3: promotes allergic inflammation and Th2 response
Contact hypersensitivity (CD):
Gal 1: increases the sensitization phase of contact hypersensitivity
Gal 1: Inhibits the elicitation phase by triggering apoptosis in T cells in the dermis
Gal 1: induces regulatory T cells and ameliorates skin inflammation
Gal 3: promotes CD response, possibly through enhancing dendritic cells migration
Gal 9: suppresses CD response. reduces Th 1 and Th 17 responses
Psoriasis:
Gal 1: suppresses Th 1 and Th 17 responses
Gal 9: reduces epidermal thickness, dermal cellular in filtrates, and the levels of cytokines in treated skin lesions

Conclusions

Galectins are now known to contribute to fundamental cellular responses in skin under normal and inflammation status and they do so by functioning inside or outside the cells. For those galectins with immunosuppressive effects, soluble recombinant proteins may be useful for treatment of autoimmune and inflammatory diseases. For those galectins implicated in diseases, their inhibitors may be used to treat these diseases. The issue is whether the proteins work inside or outside the cells, as that will determine whether the inhibitors should target intracellular or extracellular galectins. However, the functions of galectins inside and outside the cells may be difficult to distinguish.

In general, functions of galectins outside the cells may involve their carbohydrate-binding activity and those inside the cells may involve protein–protein, rather than protein–glycan interactions. The possible existence of intracellular galectin-glycan interactions has been revealed by a study suggesting that galectin-8 induces autophagosomes in macrophages infected by *Salmonella* by binding to cytosolic glycans.[59] The authors hypothesized that these glycans are present in the lumen of endosomes containing engulfed bacteria that become exposed to the cytosol after the bacteria lyse the endosomes. The glycans on the ruptured membrane can then be recognized by cytosolic galectin-8, which is followed by the formation of macromolecular complexes involving other intracellular proteins culminating in autophage. Whether binding of galectins to intracellular glycans in a similar fashion occurs under other pathological conditions and contributes to the pathogenesis of diseases remains to be delineated.

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